APPROCCI INTERDISCIPLINARI IN REUMATOLOGIA - 7a edizione

Malattie Reumatiche e Disordini Endocrino Metabolici

Torino
16 ottobre 2020

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Biostatistico
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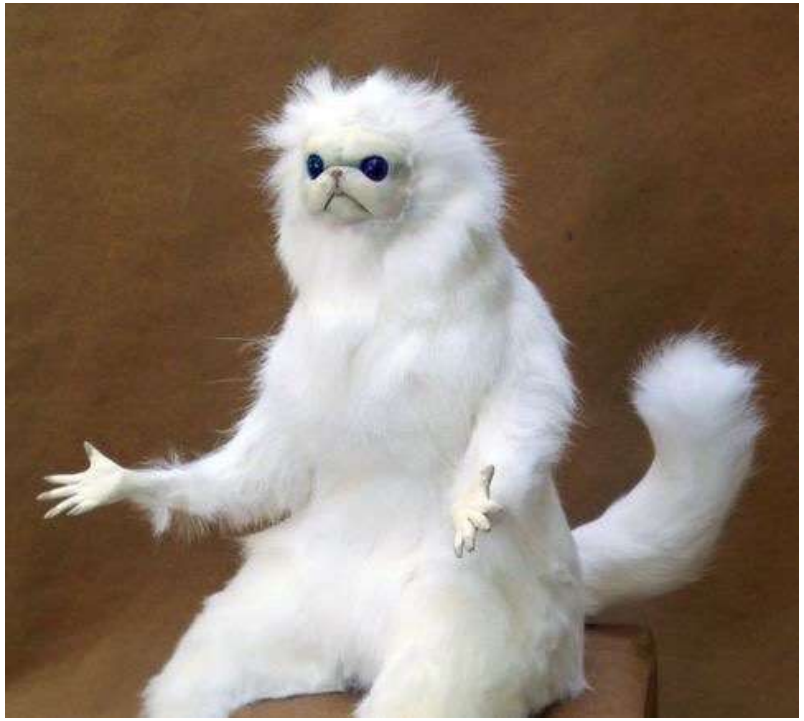
Gotta: Diagnosi e Terapia

Disclosure

I

In the last 2 years, outside this committed work:
(Personal fees) Laborest Italia Srl, Hyppocrates Sintech Srl, Pfizer, Grunenthal, Lilly, Roche.
(Grant) Italian Society of Rheumatology

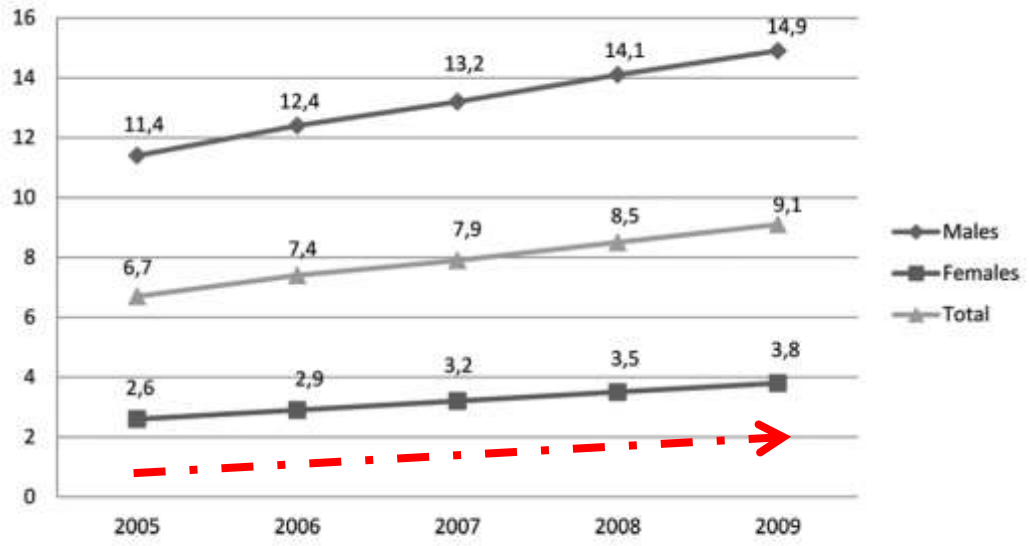
Why do we still need to talk about this?



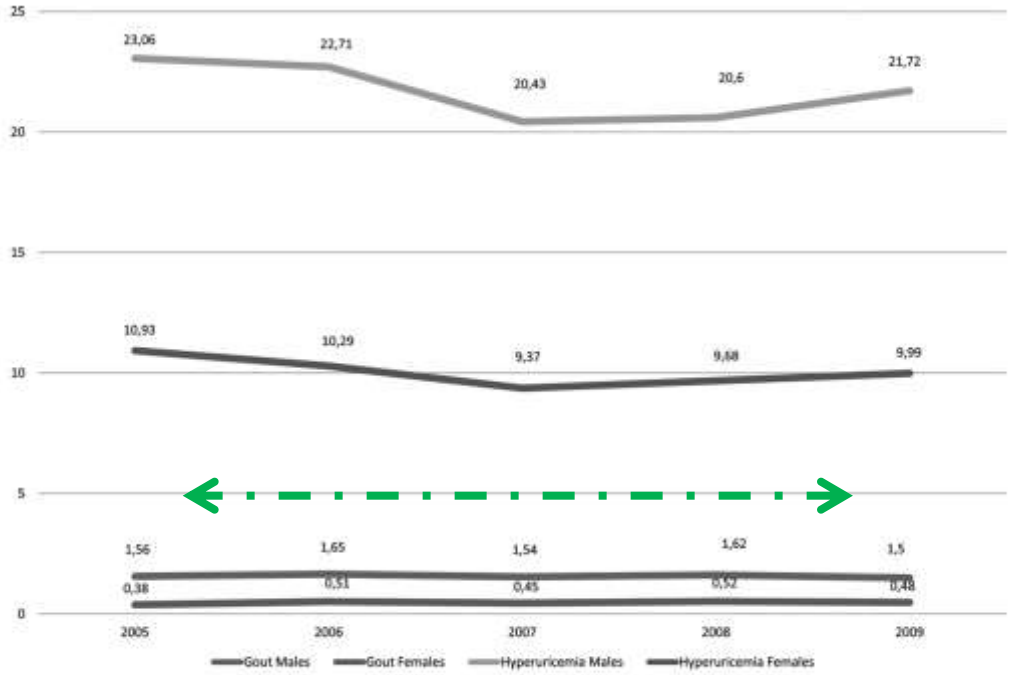
Gout: Diagnosis

Epidemiology of gout in Italy (2005-2009)

Prevalence (per 1000 ihabitants)

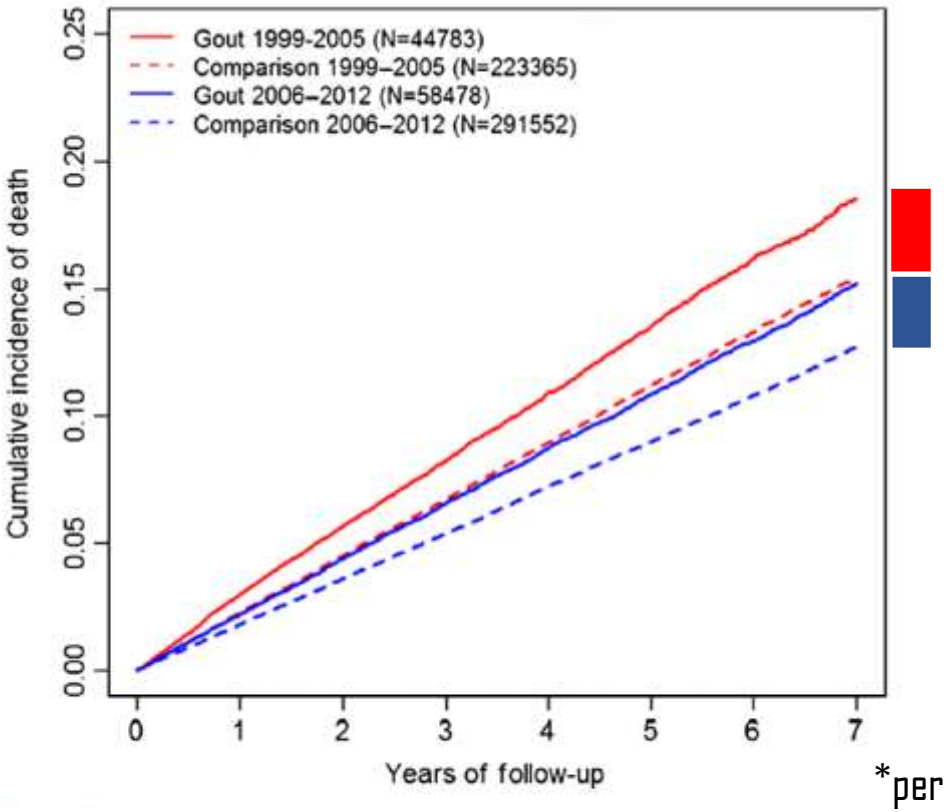


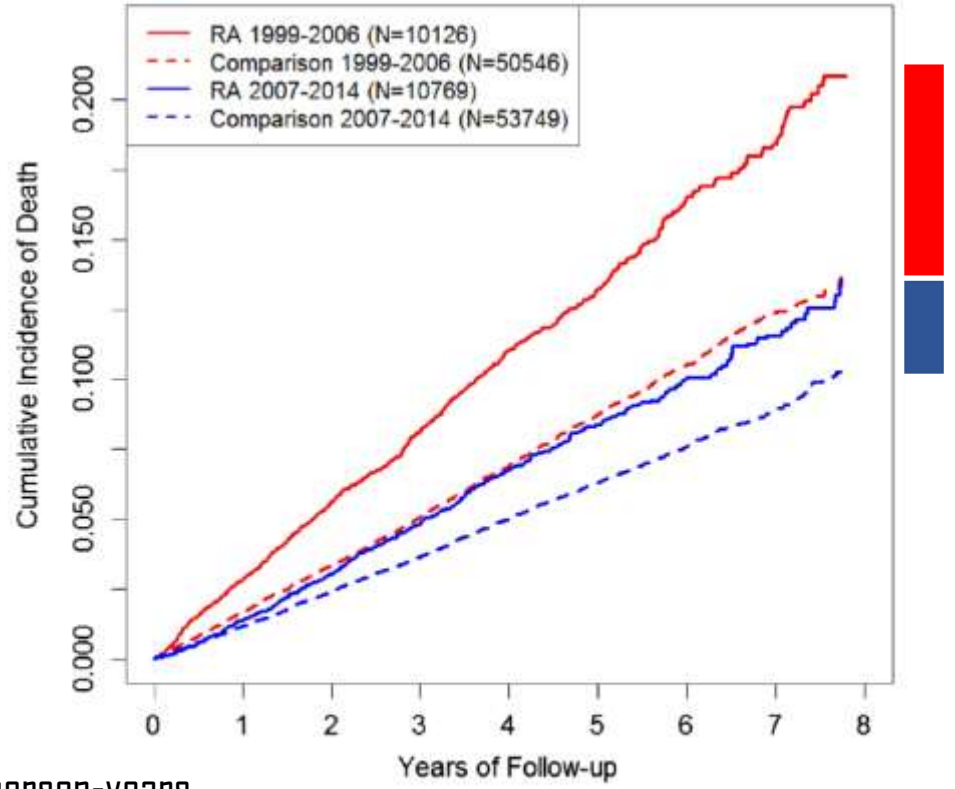
Incidence (per 1000 person-year)



Trifirò G, et al. Ann Rheum Dis 2011

Unclosing premature mortality gap





*per 1000 person-years

Fisher MC, et al. Ann Rheum Dis 2017

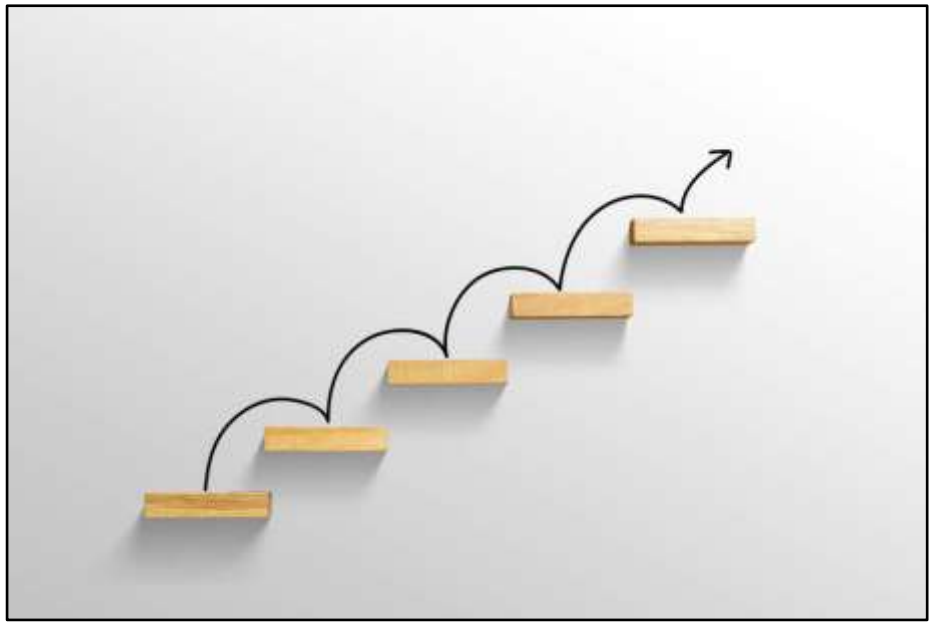
Zhang Y, et al. Ann Rheum Dis 2017

— Updated EULAR recommendation for diagnosis —

Published - January 2020

e-Published - June 2019

Evidence Update - July 2018



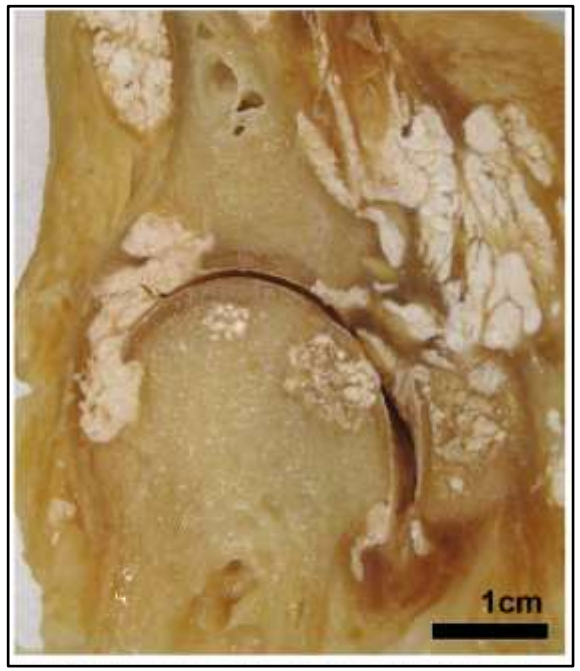
«Step-by-Step» Approach

Richette P, et al. Ann Rheum Dis 2020.

Step 1

Richette P, et al. Ann Rheum Dis 2020.

★ **Search for crystals** in SF or tophus aspirates is recommended in every person with suspected gout, because demonstration of MSU crystals allows a definitive diagnosis of gout.



Towiwat P, et al. BMC Musculoskelet Disord. 2019

It is strongly recommended that synovial fluid aspiration and examination for crystals is undertaken in any patient with undiagnosed inflammatory arthritis.

Step 2

Richette P, et al. Ann Rheum Dis 2020.

When SF analysis is not feasible,

a **clinical diagnosis** of gout is supported by

- monoarticular involvement of a foot (especially the first MTP) or ankle joint;
- previous similar acute arthritis episodes;
- rapid onset of severe pain and swelling (at its worst in <24 hours);
- erythema;
- male gender and associated cardiovascular diseases and hyperuricaemia.

These features are highly suggestive but not specific for gout.

Gout: classification criteria

Performance may be affected by **disease duration**

Criteria Set	Sensitivity	Specificity
Mexico, 2010		
Taylor *et al. 2016*		
Less than 2 years	0.87	0.66
More than 2 years	0.98	0.34
Jatuworapruk *et al. 2016*		
Less than 2 years	0.88	0.81
More than 2 years	0.99	0.30
Netherlands, 2010		
Taylor *et al. 2016*		
Less than 2 years	0.87	0.75
More than 2 years	0.96	0.47
Jatuworapruk *et al. 2016*		
Less than 2 years	0.73	0.85
More than 2 years	0.91	0.50
ACR/Eular, 2015		
Louthrenoo *et al. 2017* Clinical only		
Less than 2 years	0.74	0.91
More than 2 years	0.82	0.80
Full set (with imaging)		
Less than 2 years	0.90	0.85
More than 2 years	0.91	0.75

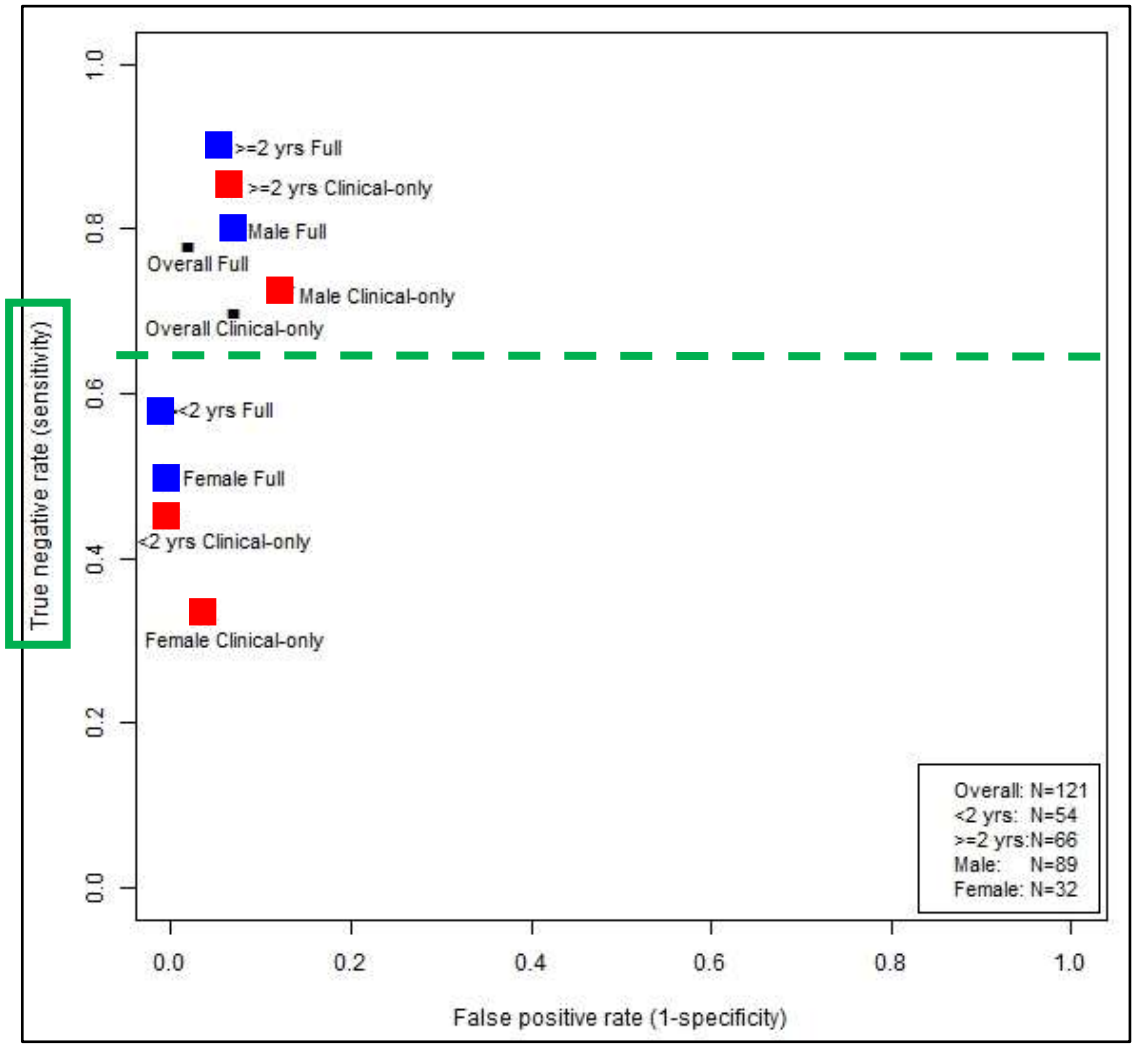
Peláez-Ballestasl, et al. J Rheumatol 2010.
Janssens HJEM, et al. Arch Intern Med 2010.
Neogi T, et al. Ann Rheum Dis 2015.
Taylor WJ, et al. Ann Rheum Dis 2016.
Jatuworapruk K, et al. Medicine 2016.
Louthrenoo W, el at. Rheumatol Int 2017.

Gout: classification criteria

ATTACk
Assessing of The diagnosis and TreAtment of Crystal-induced arthritis

SIR Società Italiana di Reumatologia

Performance may be affected
by **disease duration** and **gender**



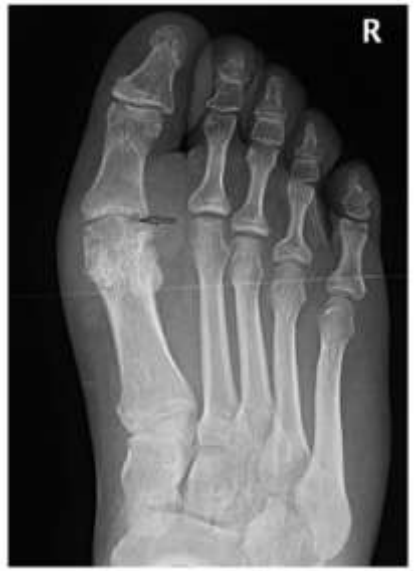
Unpublished results

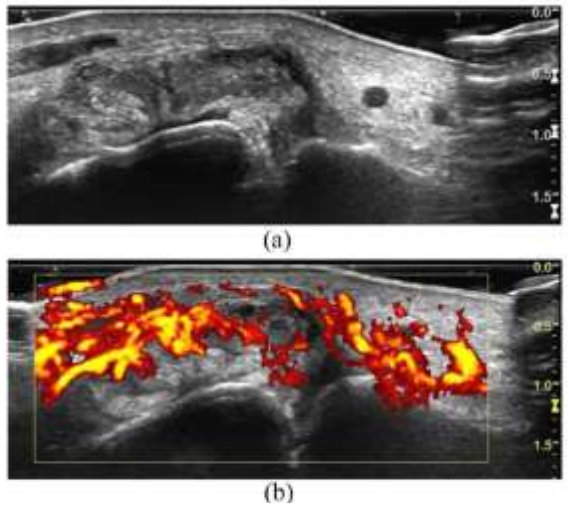
Step 3

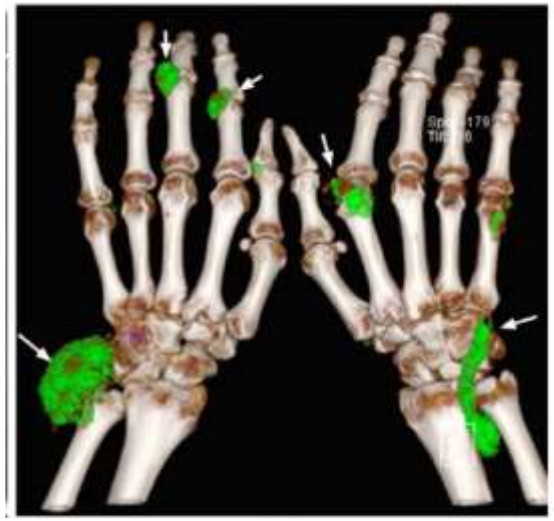
Richette P, et al. Ann Rheum Dis 2020.

When a clinical diagnosis of gout is uncertain and crystal identification is not possible,

patients should be investigated by **imaging** to search for MSU crystal deposition and features of any alternative diagnosis.



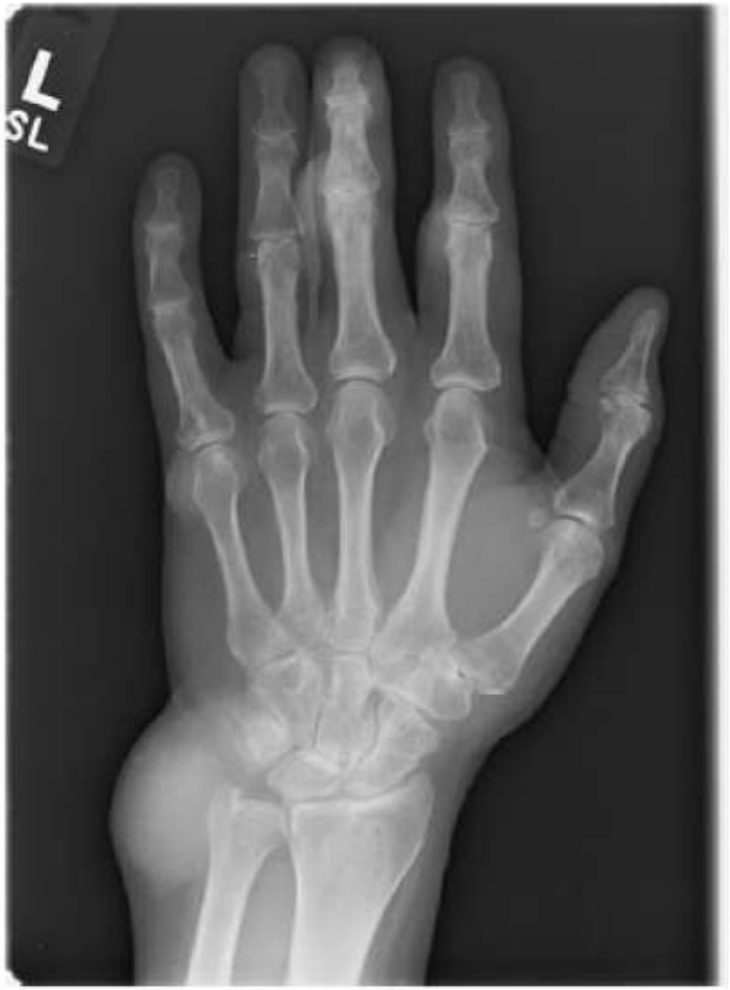




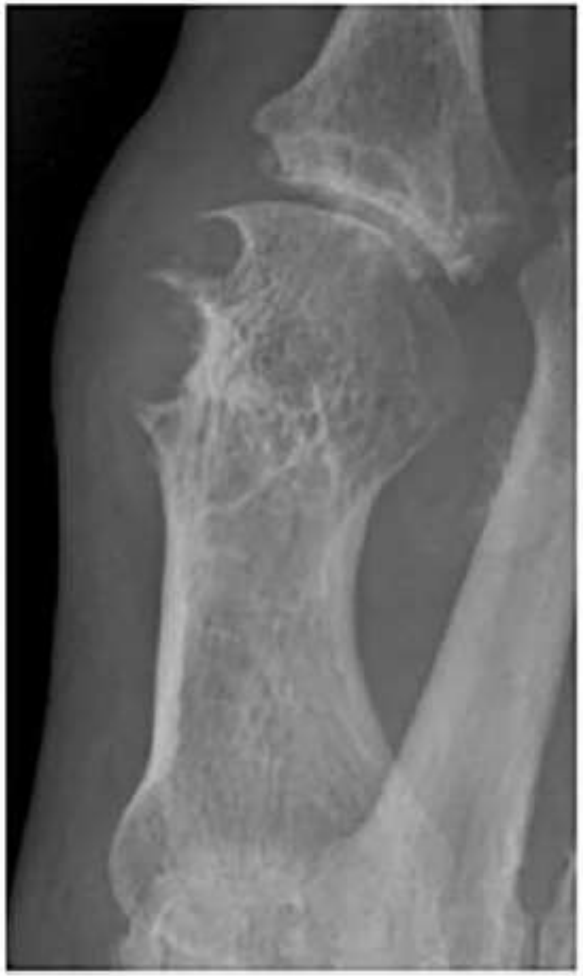
Which? still uncertainties!

Davies J, et al. Ther Adv Musculoskel Dis. 2019.

Gout: plain X-ray



Davies J, et al. Ther Adv Musculoskel Dis. 2019



Neogi T, et al. Ann Rheum Dis 2015.

to search for imaging evidence of MSU crystal deposition but have **limited** value for the diagnosis of gout flare.

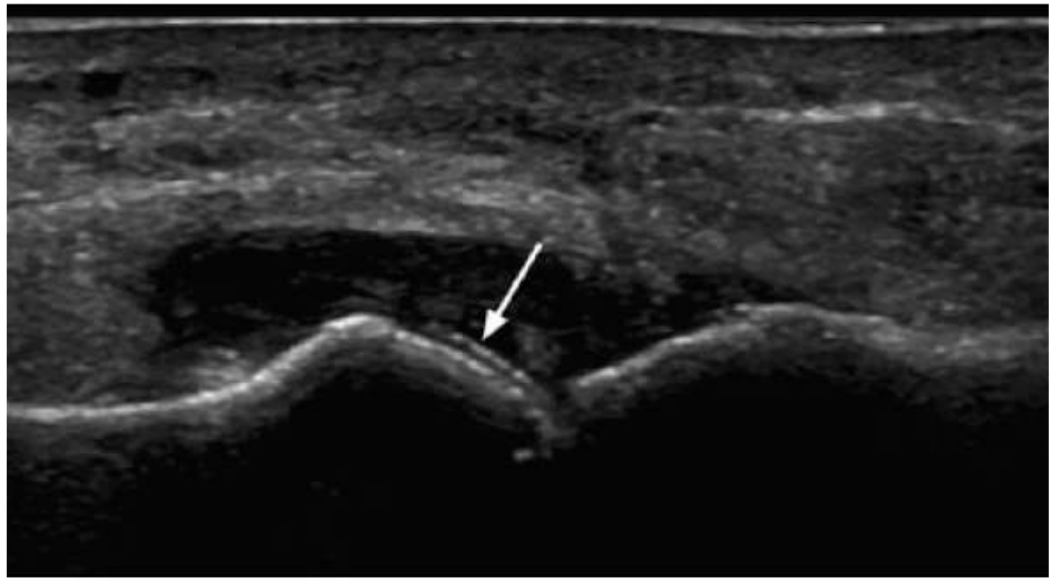
Richette P, et al. Ann Rheum Dis 2020.

Gout: ultrasonography

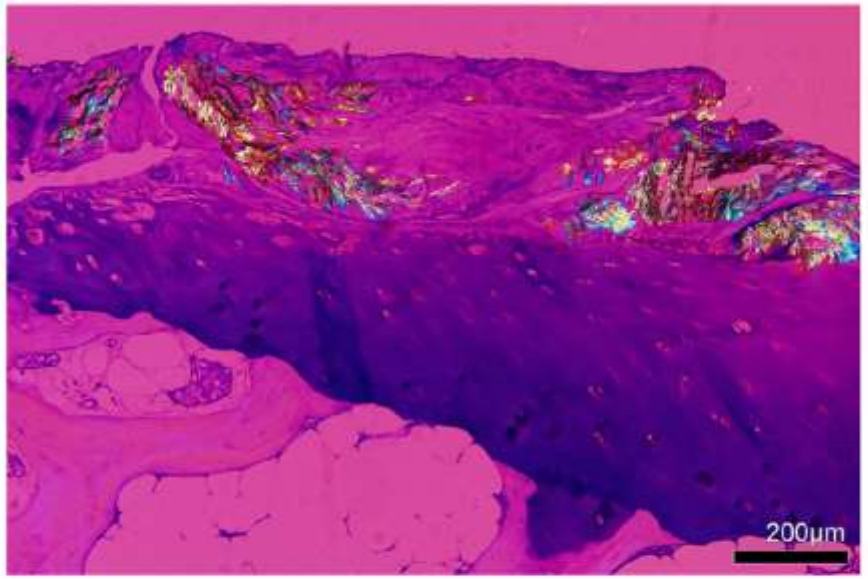
helpful in establishing a diagnosis (gout flare or chronic gouty arthritis)

- detection of tophi not evident on clinical examination,
- double contour sign at cartilage surfaces

High Specificity



Davies J, et al. Ther Adv Musculoskel Dis. 2019

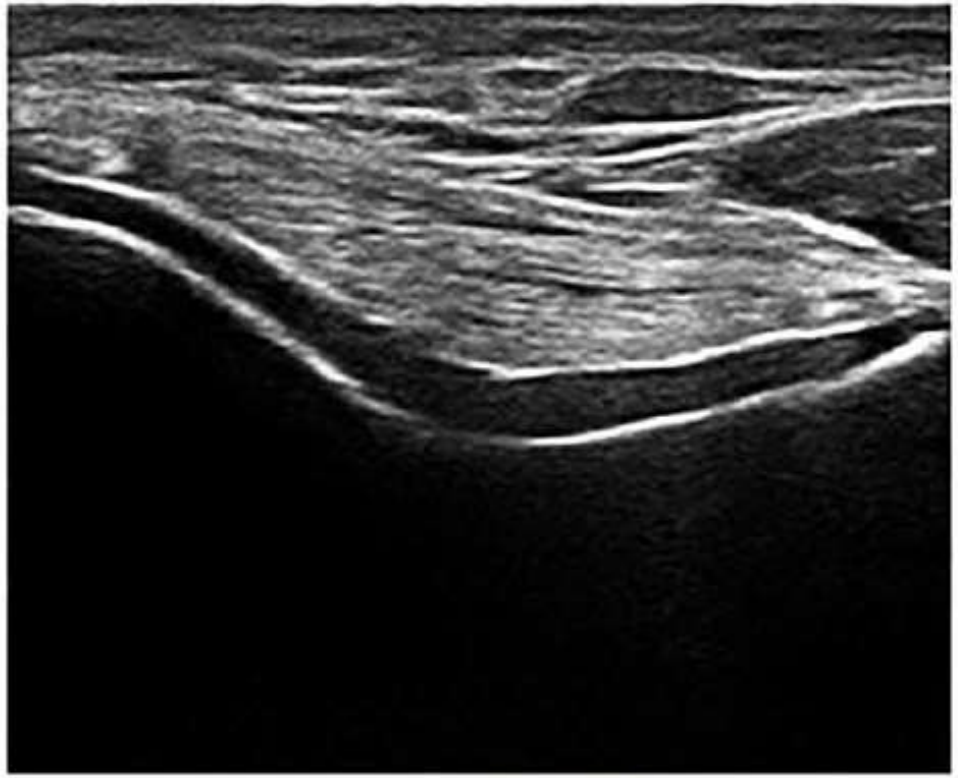


Towiwat et al. BMC Musculoskeletal Disorders. 2019

Gout: ultrasonography

High Specificity

GOUT

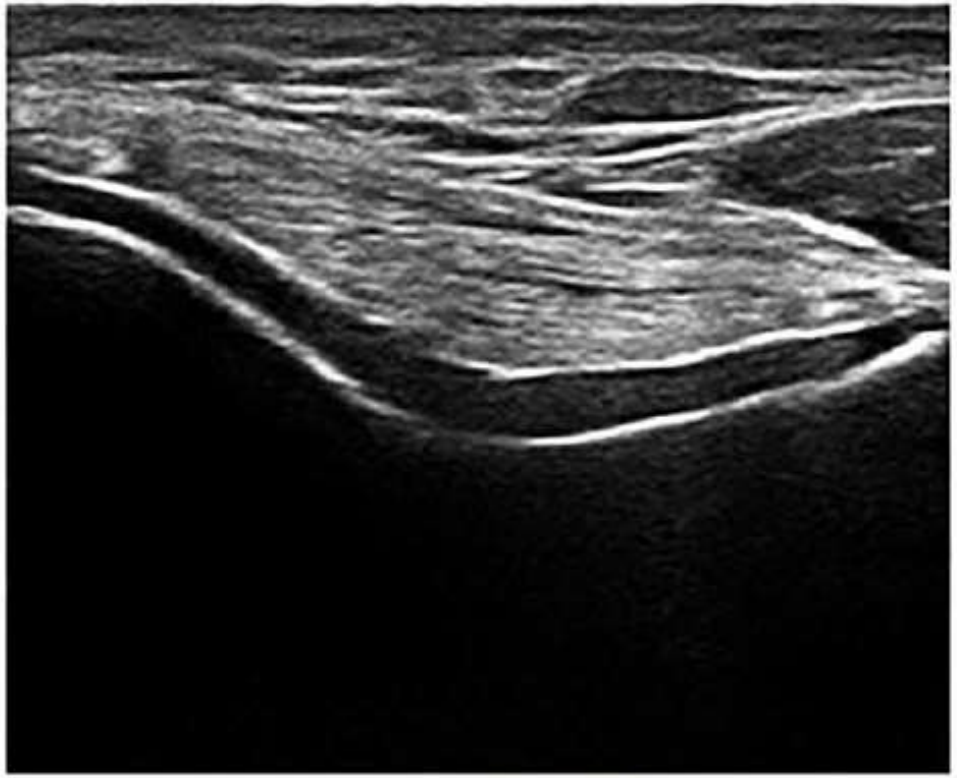


Neogi T, et al. Ann Rheum Dis 2015.

Gout: ultrasonography

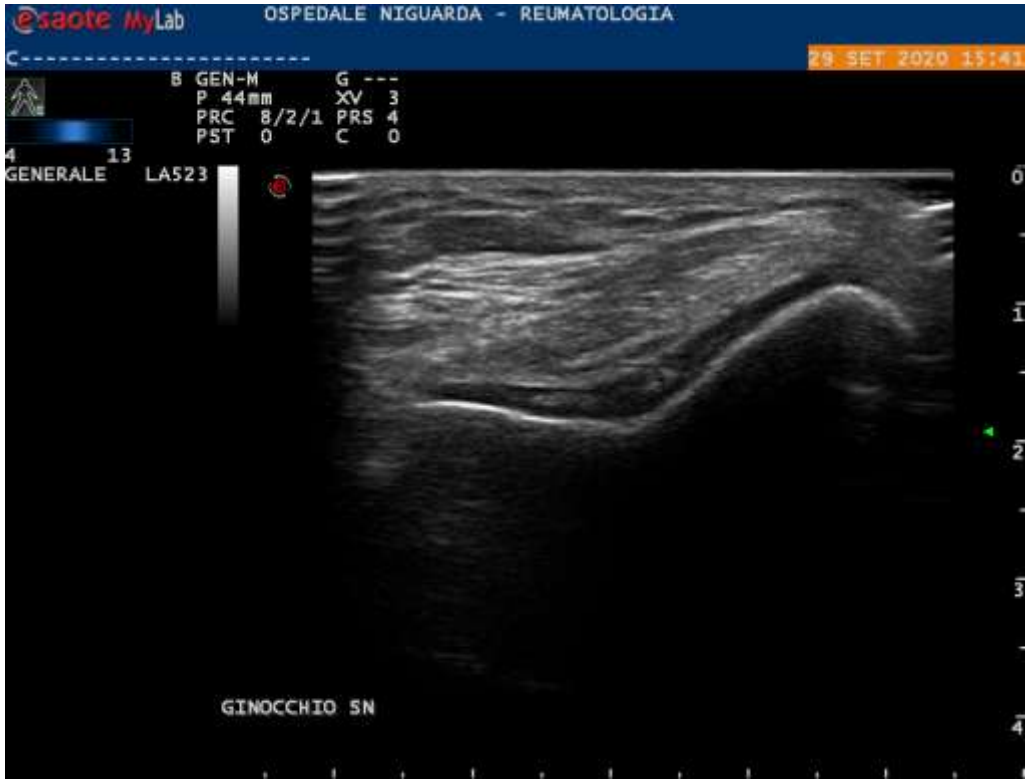
High Specificity

GOUT



Neogi T, et al. Ann Rheum Dis 2015.

~~GOUT~~ → CPPD



Gout: ultrasonography

Sensitivity !

Table 4 Sensitivity and specificity of US features for the diagnosis of gout

	Sensitivity	Specificity
Tophus		
Ogdie *et al* 2015[43] *MA**	0.65 (0.34–0.87)	0.80 (0.38–0.96)
Ogdie *et al* 2017[51]		
Early disease (<2 years)	0.33 (0.25–0.43)	0.95 (0.91–0.97)
Late disease (≥2 years)	0.50 (0.44–0.56)	0.95 (0.91–0.97)
Double contour sign		
Ogdie *et al* 2015[43] *MA†*	0.83 (0.72–0.91)	0.76 (0.68–0.83)
Ogdie *et al* 2017[51]		
Early disease (<2 years)	0.50 (0.41–0.60)	0.92 (0.87–0.95)
Late disease (≥2 years)	0.63 (0.57–0.68)	0.91 (0.86–0.94)
Snowtorm appearance		
Ogdie *et al* 2017[51]		
Early disease (<2 years)	0.32 (0.23–0.42)	0.90 (0.85–0.94)
Late disease (≥2 years)	0.29 (0.24–0.35)	0.92 (0.89–0.94)

Richette P, et al. Ann Rheum Dis 2020.

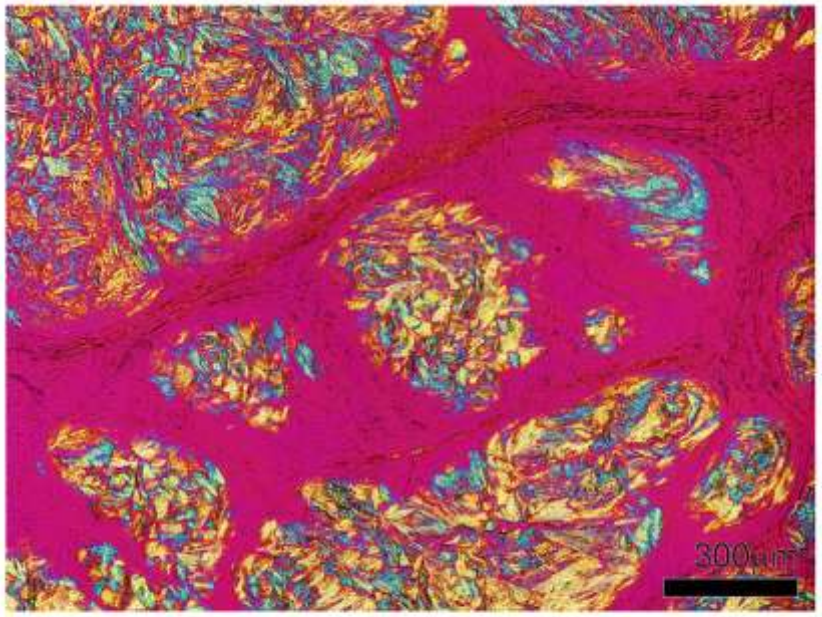
★ 17-25% positive in asymptomatic hyperuricemia !

Pineda C, et al. Arthritis Res Therapy. 2011.

Gout: Hyperuricemia & Diagnosis

The diagnosis of gout
should not be made
on the presence of
hyperuricaemia alone.

Richette P, et al. Ann Rheum Dis 2020.



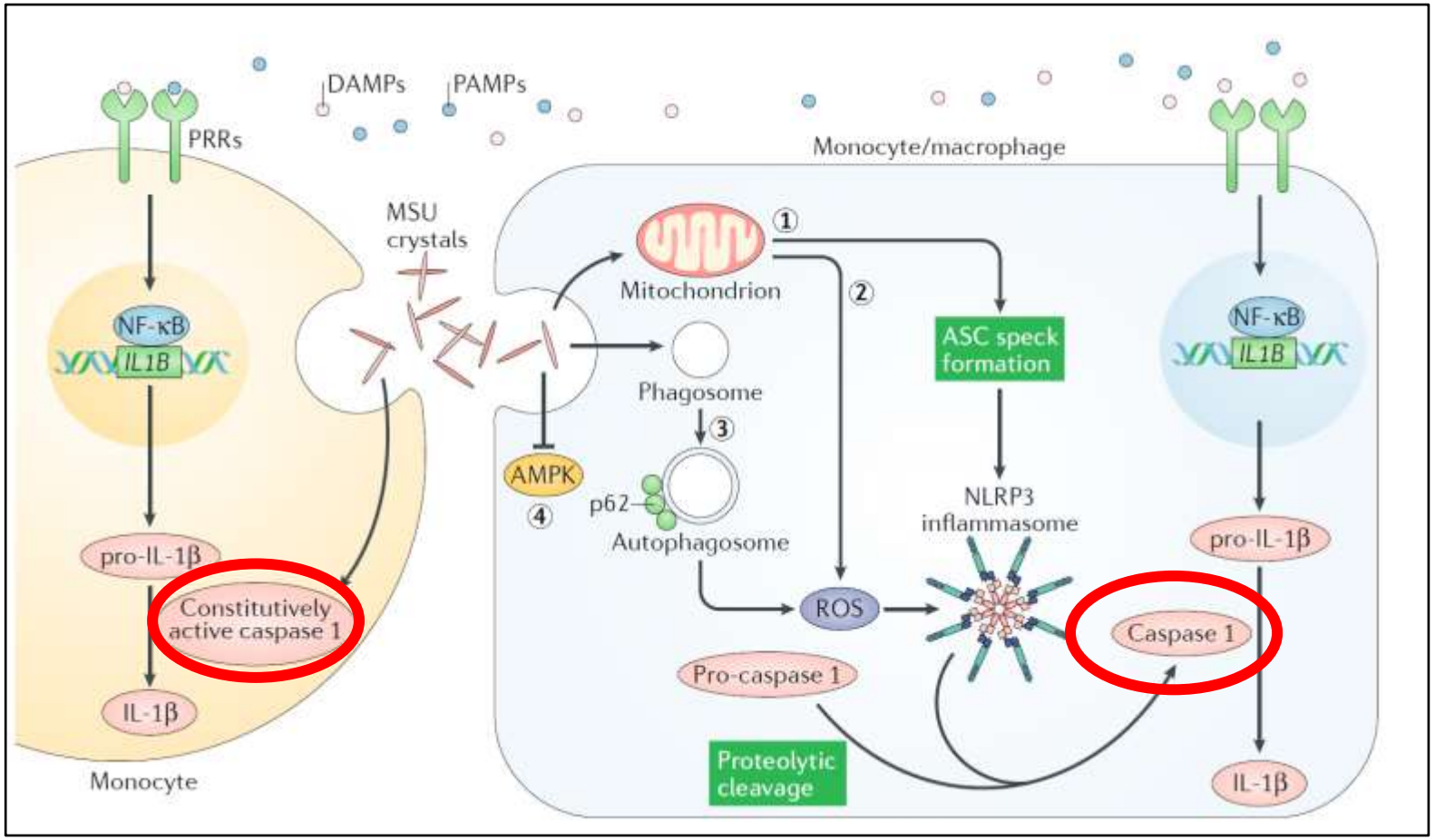
Towiwat P, et al. BMC Musculoskelet Disord. 2019

✓ **strong risk factor**

NOT as a surrogate marker for diagnosis.

Gout: Hyperuricemia & Pathogenesis

Inflammasome- dependent activation of IL-1β in response to MSU crystals



Joosten LAB, et al. Nat Rev Rheumatol. 2020

Gout: Unsolved physiopathological questions

1) Factors that trigger the symptomatic inflammatory?

Hyperuricaemia and MSU deposits are necessary but not sufficient to trigger full-blown inflammation.

2) When an attack resolves, crystals still remain in the tissues (intercritical gout) with a low-grade systemic inflammatory response in the absence of symptoms?

Step 4

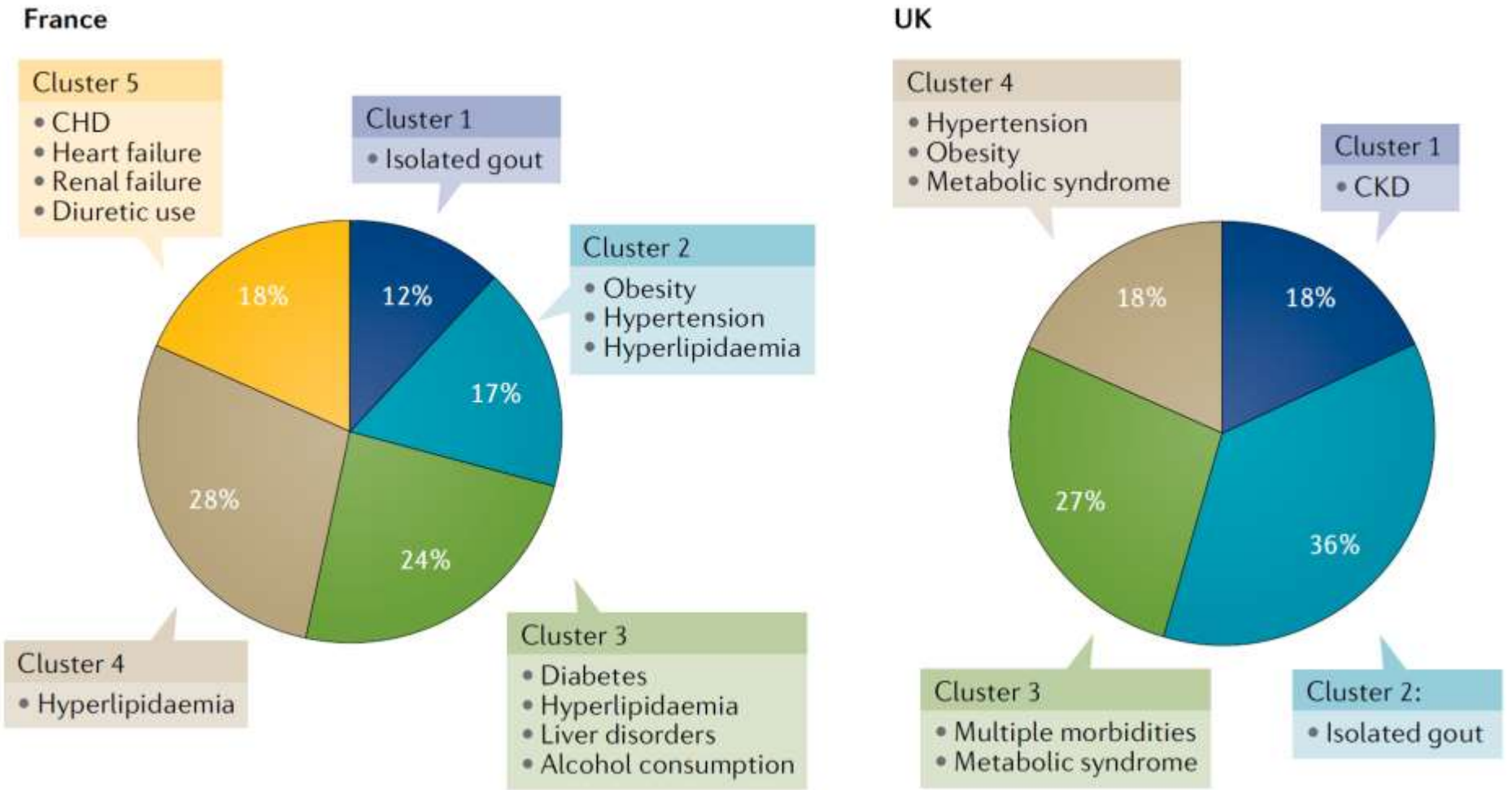
Richette P, et al. Ann Rheum Dis 2020.

Comorbidity Assessment

Associated:

- Obesity
- Renal Impairment
- Hypertension
- Ischaemic heart disease
- Heart failure
- Diabetes
- Dyslipidaemia.

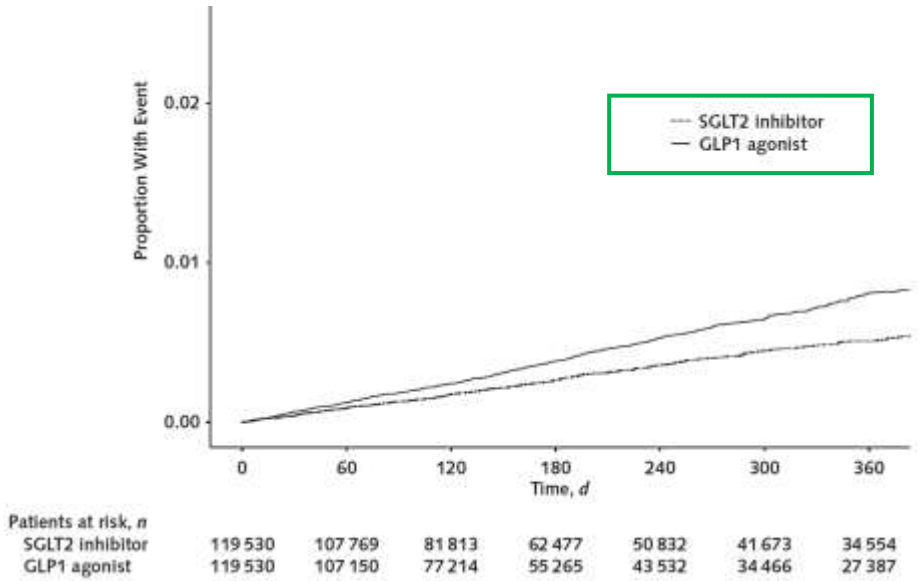
Patterns of comorbidity clustering in gout



Dehlin M, et al Nat Rev Rheum. 2020.

– Gout, Diabetes & Metabolic Syndrome –

Gout & Diabetes



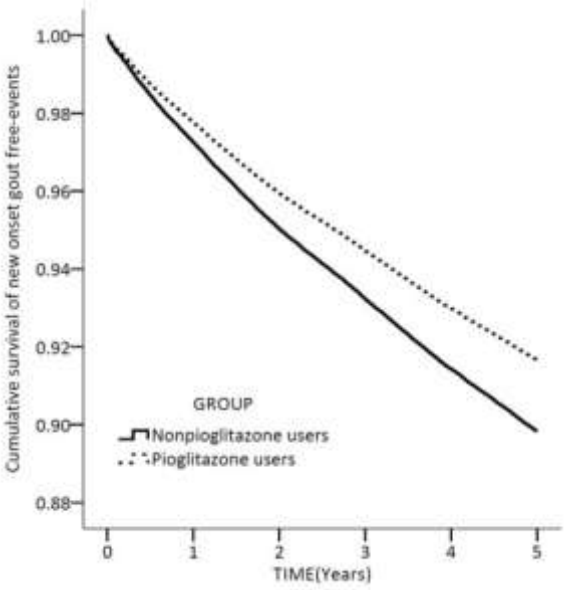
Patients at risk, *n*							
SGLT2 inhibitor	119 530	107 769	81 813	62 477	50 832	41 673	34 554
GLP1 agonist	119 530	107 150	77 214	55 265	43 532	34 466	27 387

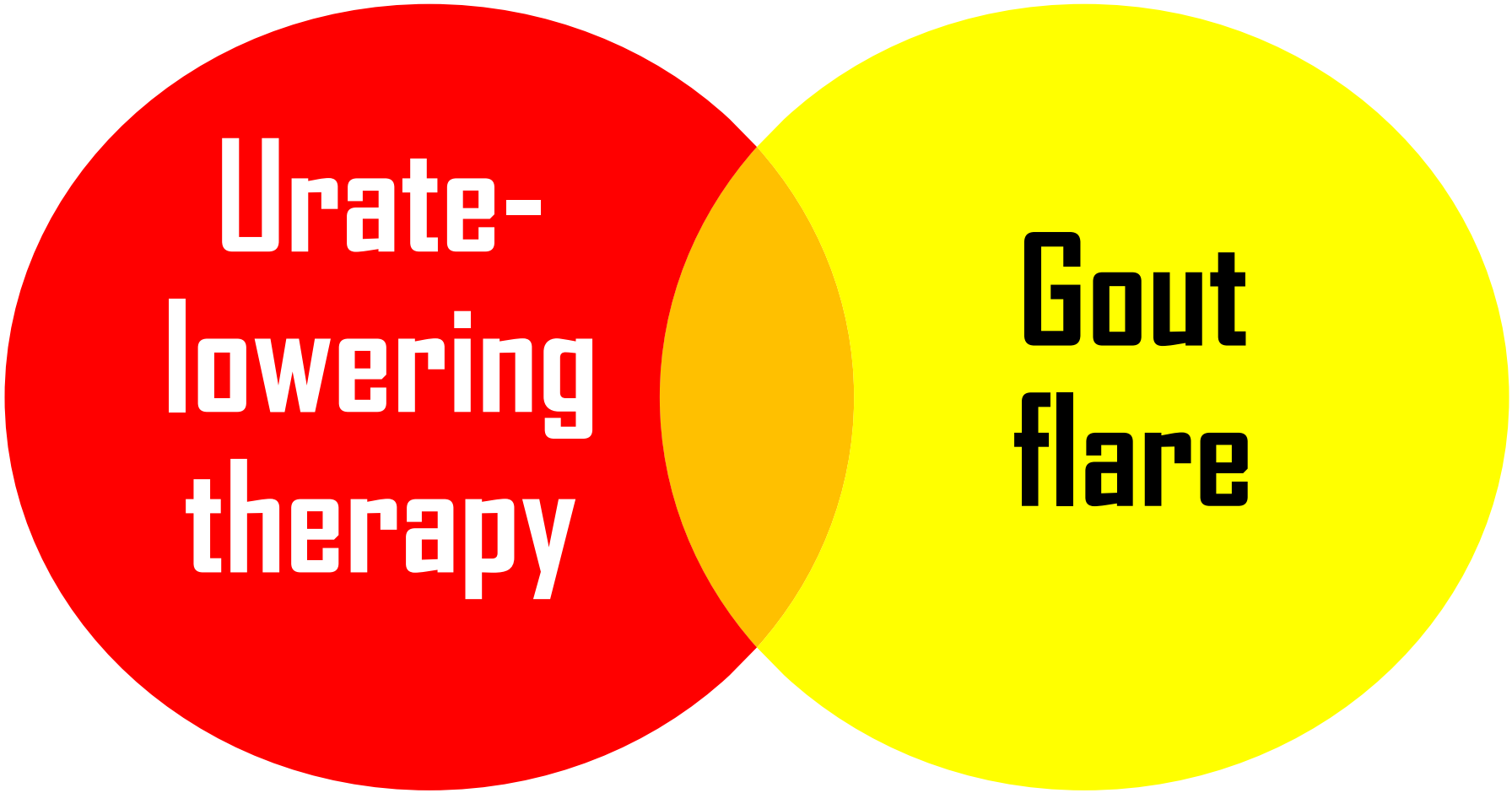
The Risk for Gout With Sodium–Glucose Cotransporter-2 Inhibitors in Patients With Type 2 Diabetes

Michael Fralick, Ann Intern Med. 2020

Decreased incidence of gout in diabetic patients using pioglitazone

Sheng-Wen Niu, Rheumatology 2018





Gout: Treatment

Clinical Practice Guidelines

Le linee guida per la pratica clinica della Società Italiana di Reumatologia (SIR) sulla diagnosi e sul trattamento della gotta

Ughi N, et al. Reumatismo. 2019.

2020 American College of Rheumatology (ACR) Guideline for the Management of Gout

FitzGerald JD, et al. Arthritis Care Res. 2020.

Urate-lowering therapy (ULT)

Start ULT

ACR 2020

Do's

≥ 2/year gout flares

- ≥ 1 tophus
- Radiographic damage
- ≥ 1 gout flare and <2 episodes/year
- SUA >9 mg/dL
- Urolothiasis
- First flare & CKD stage ≥3

Don'ts

Asymptomatic hyperuricemia

First flare with CKD stage <3

SIR 2019

Do's

Recurrent flares (>2/year)

- tophus
- Urate arthropathy (joint damage)
- SUA >8 mg/dL
- renal stones
- Comorbidities (renal impairment, hypertension, ischemic heart disease, heart failure)
- Diuretic therapy
- Diagnosis < 40 years

Urate-lowering therapy (ULT)

First-line ULT

ACR 2020

Do's

- Allopurinol
  ≤ 100 mg/day (lower in CKD)
- During the gout flare

SIR 2019

Do's

- Allopurinol
  ≤ 100 mg/day (lower in CKD)
- best delayed until
  inflammation has settled

Urate-lowering therapy (ULT)

First-line ULT

ACR 2020

Do's

- Allopurinol
  ≤ 100 mg/day (lower in CKD)
- During the gout flare

SIR 2019

Do's

- Allopurinol
  ≤ 100 mg/day (lower in CKD)
- best delayed until
  inflammation has settled

Flare prophylaxis

Do's

- Yes, 3 to 6 months
  Colchicine = NSAIDs = prednisone

Do's

- Yes, 3 to 6 months
  Colchicine > NSAIDs > prednisone

Urate-lowering therapy (ULT)

ACR 2020

Treat-to-target strategy
SUA <6 mg/dL
Life-long therapy

Target

SIR 2019

Treat-to-target strategy
SUA <6 mg/dL (if tophi < 5 mg/dL)
Life-long therapy

SUA < 3 mg/dL

Urate-lowering therapy (ULT)

Second-line ULT

ACR 2020

Do's

1º XOI > 2º XOI > XOI+uricosuric

SIR 2019

Do's

1º XOI > 2ºXOI or *XOI+uricosuric*

Urate-lowering therapy (ULT)

Second-line ULT

ACR 2020

Do's

1º XOI > 2º XOI > XOI+uricosuric

SIR 2019

Do's

1º XOI > 2ºXOI or *XOI+uricosuric*

Pegloticase

Do's

Failure of XOI treatment, uricosurics, and other interventions AND frequent gout flares (≥2 flares/year) OR who have nonresolving subcutaneous tophi

«only in patients with severe gout in whom all other forms of therapy have failed or are contraindicated»

Urate-lowering therapy (ULT)

Febuxostat

WARNING

NOTA INFORMATIVA IMPORTANTE CONCORDATA CON LE AUTORITÀ REGOLATORIE EUROPEE E L'AGENZIA ITALIANA DEL FARMACO (AIFA)

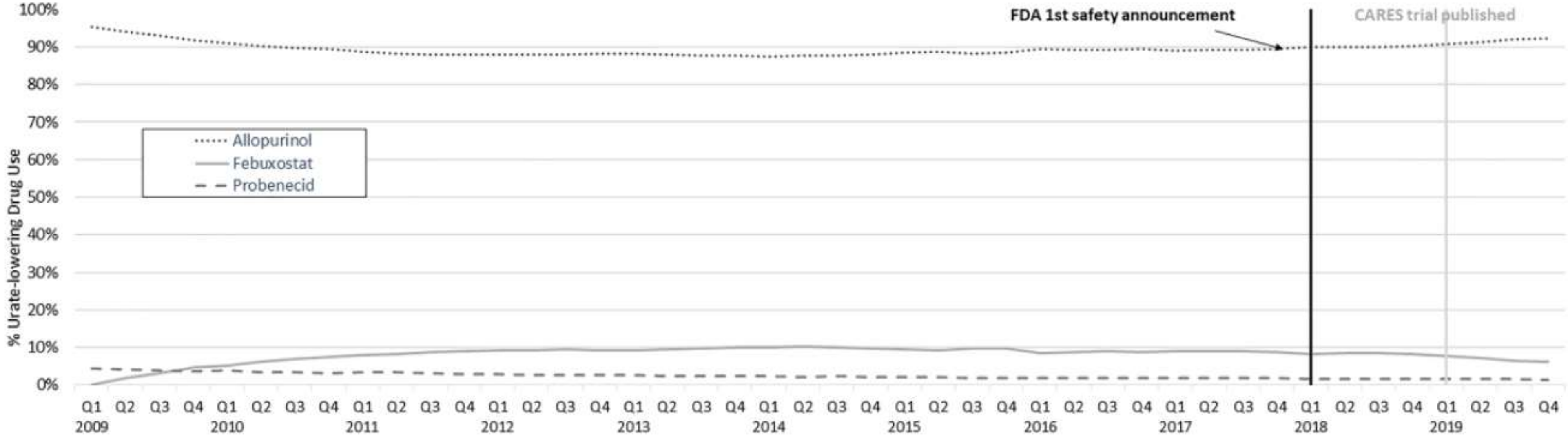
27 Giugno 2019

ADENURIC (febuxostat): aumento del rischio di morte cardiovascolare e mortalità per qualsiasi causa nei pazienti trattati con febuxostat nell'ambito dello studio CARES

«Il trattamento con febuxostat nei pazienti con malattia CV importante preesistente (ad esempio infarto miocardico, ictus o angina instabile) deve essere evitato, tranne quando non siano disponibili altre opzioni terapeutiche adeguate.»

Urate-lowering therapy (ULT)

Febuxostat
WARNING



	2009 Q1	Q2	Q3	Q4	2010 Q1	Q2	Q3	Q4	2011 Q1	Q2	Q3	Q4	2012 Q1	Q2	Q3	Q4	2013 Q1	Q2	Q3	Q4	2014 Q1	Q2	Q3	Q4	2015 Q1	Q2	Q3	Q4	2016 Q1	Q2	Q3	Q4	2017 Q1	Q2	Q3	Q4	2018 Q1	Q2	Q3	Q4	2019 Q1	Q2	Q3	Q4
Allopurinol	95%	94%	93%	92%	91%	90%	90%	89%	89%	88%	88%	88%	88%	88%	88%	88%	88%	88%	88%	88%	88%	88%	88%	88%	88%	89%	88%	88%	89%	89%	89%	89%	89%	89%	89%	89%	90%	90%	90%	90%	91%	91%	92%	92%
Febuxostat	0%	2%	3%	5%	5%	6%	7%	7%	8%	8%	9%	9%	9%	9%	9%	9%	9%	10%	10%	10%	10%	10%	10%	10%	9%	9%	10%	10%	9%	9%	9%	9%	9%	9%	9%	9%	8%	8%	8%	8%	8%	7%	6%	6%
Probenecid	5%	4%	4%	4%	4%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	1%

SC Kim, et al. Arthritis Rheumatol. 2020.

Urate-lowering therapy (ULT)

Lesinurad
WITHDRAWAL

30 June 2020

"The withdrawal is not related to any efficacy, safety or clinical concerns"

Urate-lowering therapy (ULT)

Life-style

ACR 2020

Limiting alcohol, purine, high-fructose intake
Weight loss

Adding vitamin C supplementation

SIR 2019

Reducing excess body weight, performing regular exercise, giving up smoking, avoiding excess alcohol, high purine foods, and sugar-sweetened drinks containing fructose

Expected effect on SUA → 1 mg/dl reduction only !

Emmerson BT, et al. Lancet 1991.

Gout flare management

Flare

ACR 2020

Do's

Low dose colchicine = NSAIDs = glucocorticoids (oral, intraarticular or intramuscolar)

→ ***Patient factors !***

SIR 2019

Do's

Low dose colchicine and/or an NSAID or COXIB, oral corticosteroid, articular aspiration, injection of corticosteroids.

→ ***Patient factors !***

Gout flare management

Flare

ACR 2020

- Low dose colchicine = NSAIDs = glucocorticoids (oral, intraarticular or intramuscolar)
  → *Patient factors !*
- IL-1 inhibitors only for whom antinflammatory therapies are poorly tolerated or contraindicated

SIR 2019

- Low dose colchicine and/or an NSAID or COXIB, oral corticosteroid, articular aspiration, injection of corticosteroids.
  → *Patient factors !*
- IL-1 inhibitors only in non-responders and in patients with contraindications

Gout flare management

Flare

ACR 2020

Do's

- Low dose colchicine = NSAIDs = glucocorticoids (oral, intraarticular or intramuscolar)
  → *Patient factors !*
- IL-1 inhibitors only for whom antinflammatory therapies are poorly tolerated or contraindicated
- Topical ice as adjuvant treatment

SIR 2019

Do's

- Low dose colchicine and/or an NSAID or COXIB, oral corticosteroid, articular aspiration, injection of corticosteroids.
  → *Patient factors !*
- IL-1 inhibitors only in non-responders and in patients with contraindications
- rest, elevation and exposure in a cool environment of affected joints as well as bed-cages and ice-packs

Gout management

Co-prescriptions

Effects on SUA levels

- Avoid hydroclorotiazide when feasible
- Prefer losartan when feasible
- Avoid stopping low-dose aspirin
- Avoid adding/switching to fenofibrate

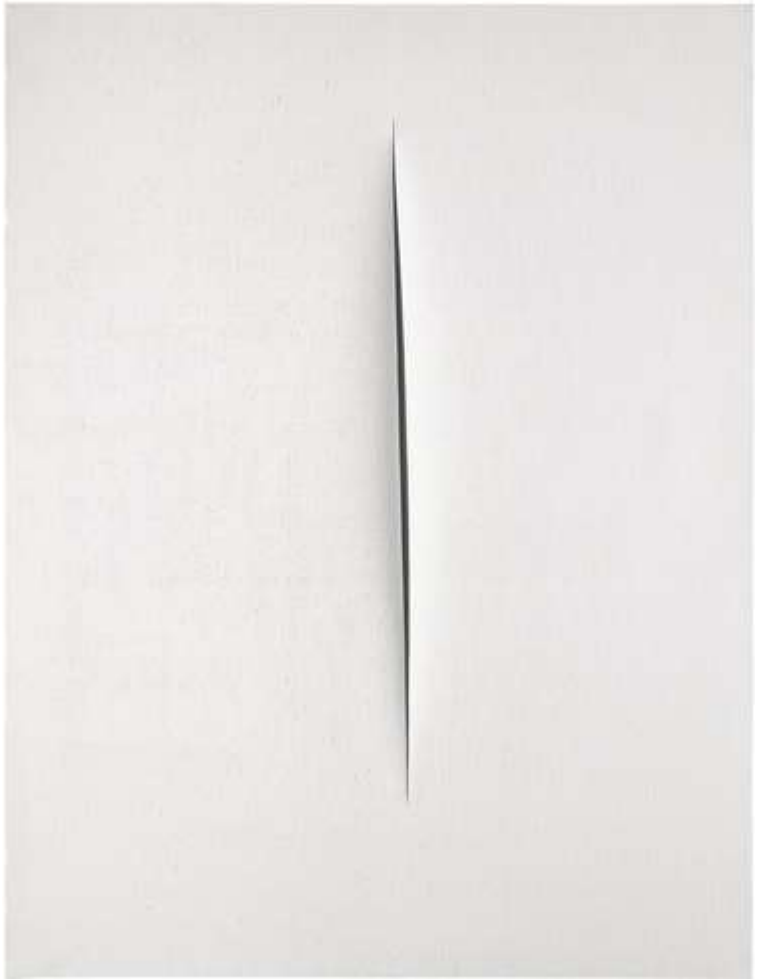
Adverse Events

- Avoid colchicine + cyclosporin or clarithromycin
- Avoid colchine in CKD and during statin treatment
- Avoid allopurinol/febuxostat + azathioprine

Take Home Messages

- Aim at a definite diagnosis!
  Rheumatologists CAN and SHOULD perform synovial fluid analysis during gout flare to detect MSU crystals
- Start ULT as soon as possible in patients with gout and recurrent flares
- Check the compliance!
- Treat-to-target strategy:
  6 (mg/dl) is the «MAGIC NUMBER»

Grazie per l'attenzione



"Scoprire il Cosmo è scoprire una nuova dimensione.

E' scoprire l'Infinito.

Così, bucando questa tela – che è la base di tutta la pittura – ho creato una dimensione infinita.

Qualcosa che per me è la base di tutta l'arte contemporanea".

Lucio Fontana (1899-1968)

Nicola Ughi
Medico specialista in Reumatologia
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